REMARKS

Applicant respectfully requests reconsideration. Claims 1-4 were previously pending in this application. Claims 1-4 are amended herein. As a result, claims 1-4 are still pending for examination with claim 1 being an independent claim. No new matter has been added.

Rejection Under 35 U.S.C. 112

Claims 1-4 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The following paragraphs address the points raised by the Examiner in the Office Action.

1) As the Examiner has articulated, the instant invention is drawn to methods for treating a subject infected with HIV by administering CpG nucleic acids.

2) The Examiner notes that the scope of the invention is broad in that the claims are drawn to treatment of a subject infected with HIV by administration of any CpG nucleic acid, while claims 2 and 3 limit the scope of the CpG nucleic acids to include additional limitations.

Applicant disagrees with the Examiner's characterization of the claimed invention as "highly unpredictable." However, Applicant has amended claims 1-4 to limit the recited CpG nucleic acids to "unmethylated CpG nucleic acids."

3) The Examiner appears to suggest that the disclosures regarding species of CpG nucleic acids, either characterized as "immunostimulatory" or "adjuvant-type," encompassed in the invention are inconsistent. Applicant respectfully disagrees. Adjuvant-type nucleic acids are a particular type of immunostimulatory nucleic acids. They are not mutually exclusive. In fact, adjuvant-type nucleic acids exert their effect, at least in part, by boosting a subject's immune system in response to a vaccine.

Contrary to the Examiner's assertion that there is a "lack of adequate working examples and the lack of guidance," Applicant contends that while working examples are not required, nevertheless the specification provides nine examples, which, taken together, sufficiently provide the basis for the claimed invention. It is widely known in the art that HIV infection causes multi-fold impairment in the subject's immune response. Naturally, medical interventions that can counteract such effects on the patient's immune system would be beneficial. Indeed, the specification provides that immunostimulatory CpG nucleic acids can, *inter alia*, stimulate B cells (see Examples), induce IL-6 production, and activate NK cells. These are hallmarks of immune stimulation. Accordingly, those skilled in the art can reasonably conclude that unmethylated CpG nucleic acids can be administered to a subject to treat HIV infection.

4) Applicant thanks the Examiner for providing a summary of published guidelines for HIV management as of 1997.

5, 6) The Examiner points to unpredictability of the art. In noting that the specification proposes using three types of CpG molecules, namely, immunostimulatory, adjuvant and IFN-α inducing molecules, the Examiner states, "It is not clear that these molecules cannot function in all three categories" (Office Action page 5-6). As specified, immunostimulatory nucleic acids are characterized by having the formula 5'-$X_1X_2CTGX_3X_4$-3'. Therefore, this encompasses the CpG nucleic acids that are categorized as adjuvant-type and/or IFN-α inducing.

The Examiner has cited several references in arguing unpredictability of the art. First, the Examiner cites Cohen & Fauci (1998) to argue that the claimed invention is not enabled. Applicant respectfully asserts that the Examiner is adopting a wrong standard. The Cohen & Fauci reference is an editorial published following an international AIDS conference, which discusses a prospect of developing "safe and effective" HIV vaccines leading to absolute cure, *i.e.*, the eradication of HIV. Applicant asserts that the issue of whether a vaccine or drug is safe is not an appropriate test for enablement. MPEP 2164.01(c). "The applicant need not demonstrate that the invention is completely safe." In fact, one cannot possibly determine the parameters of safety without a

controlled clinical trial, and it is well established that a clinical trial is not required for enablement. This is a regulatory issue that falls within a territory of the Food and Drug Administration.

Furthermore, the Cohen & Fauci reference, as well as the others cited for safety concerns, do not suggest that use of CpG would be unsafe. All drugs have some risks of side effects. The references at best suggest that care should be taken to see if there may be certain patients for which the compound might be contraindicated. This is the type of inquiry made by those of ordinary skill in the art respecting all drugs. There is no evidence in any of the cited papers that CpG nucleic acids would be unsuitable for use for treating HIV (e.g., as an adjuvant). To the contrary, the cited papers, published years after the filing date, continue to support the view that CpG oligonucleotides should be advanced through clinical trials for use as adjuvants. One of ordinary skill in the art would have believed, based on the data in the application, that CpG oligonucleotides would be well suited as clinical trial candidates for use as adjuvants. The papers cited for safety issues have not altered that view.

The authors of the Cohen & Fauci reference acknowledge that "Early optimism regarding the possibility of eradication of HIV has yielded to the more realistic concept of long-term control of virus replication." The authors then discusses the success and advances the field of HIV therapeutics has seen in recent years, which made it possible to significantly prolong survival for HIV infected individuals.

Applicant asserts that what is claimed in the instant invention is a method of *treating* a subject infected with HIV by administering an effective amount of unmethylated CpG nucleic acid. The term "treat" or "treating" is explained in the specification on page 21 last paragraph: "Reduction in viral load in the animals following the administration of the active agnets [*sic*] is indicative of the ability to reduce the viral load and thus *treat* HIV infection" (emphasis added). Thus, the instant invention does not claim to cure or eradicate HIV. Rather, the unmethylated CpG nucleic acids of the invention can contribute to an overall reduction of viral load or otherwise cause overall improvement of condition or better prognosis in an infected individual. Accordingly, Applicant asserts that the cited reference does not contradict the present invention.

Taken in its entirety, the editorial appears in fact cautiously optimistic of the outlook of effective HIV therapy, *provided that patients have adequate access, socioeconomically*, to the

available treatment. The authors state "development of a safe and effective vaccine for HIV infection remains the 'holy grail' of AIDS research" in the context of the reality that only a small fraction of the more than 30 million HIV infected patients worldwide actually has adequate medical access. In view of the foregoing, the Examiner's characterization of the editorial, "HIV therapy even many years post-filing is still hindered by inadequate treatments" is taken out of context. Furthermore, the Examiner contends that the instant claims are drawn to "any CpG nucleic acid" while "the specification teaches the CpG molecule must be unmethylated." Without acquiescing to the Examiner's characterization of the specification, Applicant has amended the claims to recite "an unmethylated CpG nucleic acid." Therefore, the claims are no longer drawn to "any" CpG nucleic acids.

The Examiner further argues, "even considering the state of the art...even unmethylated CpG nucleotides, the art is highly unpredictable...there is species selection when considering the optimal motif for immunostimulatory effects differs between species" (Office Action page 7). Specifically, the Examiner cites Agrawal (2002), MacKichan (2005), Schwarts and Oehen (2000) to support her position.

Applicant respectfully disagrees with the implied notion that such species variations amount to unpredictability or undue experimentation. Variations associated with therapeutics amongst species, or in some cases amongst individuals of the same species, are to be expected. In fact, even with an FDA-approved drug, a certain degree of optimization is required. That in itself does not render the claimed invention unpatentable. Chapter 2100 of the MPEP recites, "An applicant's specification must enable a person skilled in the art to make and use the claimed invention without undue experimentation. The fact that experimentation is complex, however, will not make it undue if a person of skill in the art typically engages in such complex experimentation." Given the amount of information provided regarding CpG nucleic acids, the skilled artisan would have no trouble implementing the claimed invention as HIV therapy.

Applicant asserts that a correlation between CpG nucleic acids and their use in the treatment of HIV infection is disclosed and enabled.

MPEP section 2164.02 teaches that:

> "[I]f the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)"

Applicant has presented data and believes that it correlates with the scope of the claimed invention.

The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *In re* Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). In Wands the court observed that "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed . . . ." Id. Contrary to the Examiner's assertion that there is a "lack of guidance," Applicant respectfully contends that adequate guidance is provided to the direction in which the experimentation should proceed such that those skilled in the art can use the claimed invention for treating HIV. The skilled artisan would know how to make and prepare a composition comprising an unmethylated nucleic acid as described in the specification as filed. In addition, the skilled artisan would know how to optimize the same, based on the various parameters as presented in the examples to assay immune responses in a subject.

The Examiner cites Oehen et al (2000) to support the argument that "CpG was not able to produce CTL protective responsive [*sic*]" (Office Action page 8). The cited reference narrowly focuses on a specific type of vaccine and its effectiveness in a specific context related to LCMV. The data presented in this sole article in itself should not be the basis for construing that immunostimulatory CpG nucleic acids are generally ineffective. In fact, the Oehen reference recites

a number of studies in which immunostimulatory sequences were successfully employed for effective immunization (see Introduction; page 163 of the Oehen reference: "immunostimulatory sequences (ISS) containing CpG motifs have been associated with effective immunization"). In addition, data from the cited reference merely showed that the immunostimulatory nucleic acid was coupled to gold beads, but did not positively show that the immunostimulatory nucleic acid was actually active and available in vivo, in such a way that the molecules can bind to and stimulate TLR receptors, since the data did not provide any positive control. Thus, concluding that unmethylated CpG nucleic acids are ineffective based on the reference appears premature. Furthermore, even if the conclusions obtained in this specific experimental context were confirmed, that in itself would not be a sufficient basis for rejecting the claims, because the instant claims relate to HIV and this reference relates to a specific example of LCMV.

In view of the foregoing, Applicant asserts that the claimed invention is enabled. Accordingly, Applicant respectfully requests that the rejection made under 35 U.S.C. § 112 be withdrawn.

Double Patenting Rejection

Claims 1 and 2 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 37-56 of copending Application No. 10/788,191.

Applicant respectfully requests that this rejection be held in abeyance since the copending claims have not yet been allowed.

Claim 1 has been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 37, 45, 46, 50, 56-58 of co-pending Application No. 11/067,516.

Applicant respectfully requests that this rejection be held in abeyance since the co-pending claims have not yet been allowed.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

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Respectfully submitted,

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